

(19) 世界知的所有権機関
国際事務局(43) 国際公開日
2003 年 8 月 28 日 (28.08.2003)

PCT

(10) 国際公開番号
WO 03/070686 A1

(51) 国際特許分類: C07C 69/734,
59/62, 59/68, 229/42, 205/56, 233/54, 235/06, 235/16,
235/20, 237/20, 275/42, 311/08, 311/29, 317/46, 307/10,
A61K 31/192, 31/216, 31/235, 31/255, 31/341, 31/381,
31/404, 31/421, 31/428, 31/44, 31/4406, 31/47, 31/4353,
31/4402, A61P 25/04, 29/00, 37/02, 37/08, 43/00, C07D
209/08, 209/12, 213/30, 215/14, 215/22, 263/32, 277/62,
277/68, 277/72, 277/82, 307/42, 307/68, 307/79, 333/54,
409/12, 217/02, 217/24, 231/12

富士市 森島 5 1 6-1 Shizuoka (JP). 栗山 浩
(KURIYAMA, Hiroshi) [JP/JP]; 〒417-0801 静岡県 富
士市 大淵 2 0 5-8 Shizuoka (JP).

(74) 代理人: 特許業務法人特許事務所サイクス (SIKS &
CO.); 〒104-0031 東京都 中央区 京橋一丁目 8 番 7 号
京橋日殖ビル 8 階 Tokyo (JP).

(21) 国際出願番号: PCT/JP03/01849

(22) 国際出願日: 2003 年 2 月 20 日 (20.02.2003)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願 2002-45293 2002 年 2 月 21 日 (21.02.2002) JP
特願 2002-301543
2002 年 10 月 16 日 (16.10.2002) JP

(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB,
BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK,
DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ,
OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
ZM, ZW.

(84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ,
SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア特許 (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許
(AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB,
GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI
特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG).

(71) 出願人 (米国を除く全ての指定国について): 旭化
成株式会社 (ASAHI KASEI KABUSHIKI KAISHA)
[JP/JP]; 〒530-8205 大阪府 大阪市北区 堂島浜 1 丁目
2 番 6 号 Osaka (JP).

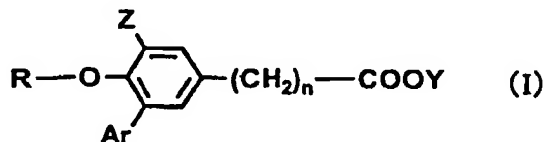
添付公開書類:
— 国際調査報告書

(72) 発明者; および
(75) 発明者/出願人 (米国についてのみ): 正田 基
(SHODA, Motoshi) [JP/JP]; 〒416-0948 静岡県

2 文字コード及び他の略語については、定期発行される
各 PCT ガゼットの巻頭に掲載されている「コードと略語
のガイダンスノート」を参照。








(54) Title: SUBSTITUTED PHENYLALKANOIC ACID DERIVATIVE AND USE THEREOF

(54) 発明の名称: 置換フェニルアルカン酸誘導体及びその用途



(57) Abstract: A compound represented by the general formula (I): [wherein n is an integer of 1 to 3; R represents C₃₋₈ alkyl, a group represented by R¹(CH₂)_k (k is an integer of 0 to 3; and R¹ represents C₃₋₇ saturated cycloalkyl or C₆₋₈ fused-ring saturated alkyl, provided that R¹ may be substituted by C₁₋₄ alkyl), etc.; and Ar represents a bicyclic fused-ring group, e.g., naphthalen-1-yl] or a salt of the compound. The compound or salt has prostaglandin and leukotriene production inhibitory activity. It is useful for the prevention of and treatments for, e.g., various inflammatory diseases attributable to the lipid mediator.

[続葉有]

Available features	
1 / 1 FAMPAT - Patent Families - ?QUESTEL-ORBIT	
CA2477208 - SUBSTITUTED PHENYLALKANOIC ACID DERIVATIVE AND USE THEREOF	
FAN	20042802068059
PN	 CA2477208 A1 20030828 [CA2477208]  WO03070686 A1 20030828 [WO200370686]  AU2003211384 A1 20030909 [AU2003211384]  US2004044258 A1 20040304 [US20040044258]  EP1477472 A1 20041117 [EP1477472] MXPA04008176 A 20041126 [MXPA04008176]  US6867320 B2 20050315 [US6867320] CN1653032 A 20050810 [CN1653032]  EP1477472 A4 20051214 [EP1477472]
TI	SUBSTITUTED PHENYLALKANOIC ACID DERIVATIVE AND USE THEREOF
PA	ASAHI CHEMICAL IND ASAHI KASEI PHARMA CORP KURIYAMA HIROSHI SHODA MOTOSHI
PA0	Asahi Kasei Pharma Corporation; 9-1, Kanda Mitoshiro-cho Chiyoda-ku; Tokyo 101-8481 (JP)
IN	SHODA MOTOSHI; KURIYAMA HIROSHI
AP	2003CN-0808999 20030220 2003AU-0211384 20030220 2003EP-0706983 20030220 2003CA-2477208 20030220 2003US-0368435 20030220 2003WO-JP01849 20030220 2004MX-PA08176 20040820
FD	(US20040044258) Prov. AP US60419098 20021018 [2002US-P419098] Prov. AP US60358337 20020222 [2002US-P358337]
PR	2002JP-0045293 20020221 2002JP-0301543 20021016 2002US-P358337 20020222 2002US-P419098 20021018 2003US-0368435 20030220 2003WO-JP01849 20030220
IC	A61K-031/19 A61K-031/192 A61K-031/215 A61K-031/216 A61K-031/235 A61K-031/255 A61K-031/341 A61K-031/381 A61K-031/404 A61K-031/405 A61K-031/41 A61K-031/421 A61K-031/425 A61K-031/428 A61K-031/4353 A61K-031/44 A61K-031/4402 A61K-031/4406 A61K-031/47 A61P-025/04 A61P-029/00 A61P-037/00 A61P-037/02

	A61P-037/08 A61P-043/00 C07C-027/00 C07C-059/00 C07C-059/62 C07C-059/68 C07C-059/72 C07C-062/06 C07C-069/00 C07C-069/734 C07C-069/76 C07C-205/56 C07C-229/00 C07C-229/42 C07C-233/00 C07C-233/54 C07C-235/06 C07C-235/16 C07C-235/20 C07C-237/20 C07C-275/42 C07C-307/00 C07C-307/10 C07C-311/08 C07C-311/29 C07C-317/46 C07D-209/00 C07D-209/08 C07D-209/12 C07D-209/18 C07D-213/30 C07D-215/14 C07D-215/22 C07D-217/02 C07D-217/24 C07D-231/12 C07D-231/56 C07D-263/32 C07D-277/62 C07D-277/64 C07D-277/68 C07D-277/72 C07D-277/82 C07D-307/42 C07D-307/68 C07D-307/79 C07D-333/54 C07D-333/60 C07D-409/12
ICAA	C07C-059/72 [2006-01 A - I R M EP]; C07C-069/734 [2006-01 A - I R M EP]; C07C-229/42 [2006-01 A - I R M EP]; C07C-307/10 [2006-01 A - I R M EP]; C07D-209/08 [2006-01 A - I R M EP]
ICCA	C07C-059/00 [2006 C - I R M EP]; C07C-069/00 [2006 C - I R M EP]; C07C-229/00 [2006 C - I R M EP]; C07C-307/00 [2006 C - I R M EP]; C07D-209/00 [2006 C - I R M EP]
EC	C07C-059/58 C07C-059/68 C07C-059/72 C07C-069/734 C07C-229/42 C07C-307/10 C07D-209/08 C07D-209/18
ICO	M07C-101/08
PCL	ORIGINAL (O) : 560056000; CROSS-REFERENCE (X) : 562466000 564172000
DS	(EP1477472) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT SE SI SK TR

	AL LT LV MK RO
DS	(WO200370686) AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW European patent (AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR) OAPI patent (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG) ARIPO patent (GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW) Eurasian patent (AM AZ BY KG KZ MD RU TJ TM)
CT	(EP1477472) Cited in the search report TAMURA Y: "NONSTEROIDAL ANTIINFLAMMATORY AGENTS. 1. 5-ALKOXY-3- BIPHENYLYLACETIC ACIDS AND RELATED COMPOUNDS AS NEW POTENTIAL ANTIINFLAMMATORY AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 20, no. 5, 1977, pages 709-714, XP002025861 ISSN: 0022-2623(Cat. A) See also references of WO 03070686A1
CT	(US20040044258) Cited; US4873259; US5136090; US5155259; US5232948; US5237091; US5262565; US5319139; US5391817; US5462954; US5478857; US5482941; US5563164; US5994379; US6147100; US6200980; US6376546; US20020161022; EP0499926; WO9307149; WO0035886
CT	(WO200370686) Cited in the search report EP1024130(A1)(Cat. A);WO9626921(A1)(Cat. A) See also references of EP 1477472A1
AB	(EP1477472) A compound represented by the formula (I) or a salt thereof wherein n represents an integer of 1 to 3, R represents an alkyl group having 3 to 8 carbon atoms, a group represented by the following formula: R**1 (CH ₂) _k - (wherein k represents 0 or an integer of 1 to 3; R**1 represents a saturated cyclic alkyl group having 3 to 7 carbon atoms or a saturated condensed cyclic alkyl group having 6 to 8 carbon atoms, and the group R**1 may be substituted with a lower alkyl group having 1 to 4 carbon atoms) and the like, and Ar represents a condensed bicyclic group such as naphthalen-1-yl group, which has suppressing action on prostaglandin and leukotriene production and is useful for prophylactic and/or therapeutic treatment of various inflammatory diseases and the like caused by these lipid mediators.
OBJ	(EP1477472) The present invention relates to a novel substituted phenylalkanoic acid derivative. An object of the present invention is to provide compounds that inhibit production of prostaglandins and leukotrienes to prevent and/or cure various kinds of inflammatory diseases, autoimmune diseases, allergic diseases, and pain in mammals resulting from the lipid mediators. The present invention thus provides a compound represented by the formula (1) or a salt thereof: (see diagramm 1 page 5) wherein n represents an integer of 1 to 3, R represents a linear or branched alkyl group having 3 to 8 carbon atoms, a group Ra represented by the following formula: R**1 (CH ₂) _k - or a group Rb represented by the following formula: (see diagramm 2 page 5) wherein k in the substituent Ra represents 0 or an integer of 1 to 3; R**1 represents a saturated cyclic alkyl group having 3 to 7 carbon atoms or a saturated condensed cyclic alkyl group having 6 to 8 carbon atoms, and the group R**1 may be substituted with a lower alkyl group having 1 to 4 carbon atoms; Q in the group Rb represents a monocyclic or bicyclic aryl group, and Q may contain 1 or 2 heteroatoms; A**1 represents a single bond or an alkylene (a) having 1 to 3 carbon atoms, and the alkylene (a) may be substituted with a lower alkyl group having 1 to 4 carbon atoms or phenyl group; A**2 represents a single bond, oxygen atom, sulfur atom, -S(O)-, -S(O) ₂ -, or -N(R**4) - (wherein, when A**2 represents oxygen atom, sulfur atom, -S(O)-, -S(O) ₂ -, or -N(R**4) -, A**1 represents ethylene or trimethylene); R**2 and R**3 both or each independently represent hydrogen atom, a linear or branched saturated alkyl group having 1 to 4 carbon atoms, phenyl group, fluorine atom, chlorine atom, bromine atom, trifluoromethyl group, an -OR**5 group, an -N(R**6) ₂ group, an -NHCOR**7 group, or an NHSO ₂ R**8 group, wherein R**4, R**6 and R**7 each independently represent hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms, and R**5 and R**8 represent a lower alkyl group having 1 to 4 carbon atoms; Z represents hydrogen atom, fluorine atom, chlorine atom, nitro group, amino group, methyl group, or an OR**9 group wherein R**9 represents hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms;
ADB	(EP1477472) For example, in a pathological tissue of rheumatoid arthritis, which is an autoimmune disease and is one of chronic inflammatory diseases, expression of COX-2 and production of PGE ₂ or TXA ₂ as well as expression of 5-LO and production of LTB ₄ are observed [Bonnet et al., Prostaglandins, 1995, vol. 50, p.127]. In a mouse deficient in FLAP which is a protein required for activation of 5-LO, symptoms of collagen-induced arthritis, as a disease model of chronic rheumatoid arthritis, are reported to be milder compared with those in a wild-type mouse [Griffiths et al., J. Exp.

	<p>Dis, 1990, vol. 142, p.112], and airway hypersensitivity, which is a disease model of bronchial asthma, is reported to unlikely occur in a PGD2 receptor deficient mouse [Matsuoka et al., SCIENCE, 2000, vol. 287, p.2013]. Accordingly, roles of prostaglandins and leukotrienes are demonstrated to be important in bronchial asthma.</p> <p>In a pathological tissue of Alzheimer's disease, which is one of diseases accompanied by neurodegeneration, it is demonstrated that COX activity and 5-LO activity are increased, and prostaglandins and leukotrienes cause formation of beta -amyloid proteins which constitute one class of pathogenic substances of Alzheimer's disease to induce degeneration of nerve cells [Sugaya et al., Jpn. J. Pharmacol., 2000, vol. 82, p.85]. Thus, it is considered that prostaglandins and leukotrienes are responsible for important roles in formation of neurodegenerative diseases such as Alzheimer's disease.</p>
ICLM	<p>(EP1477472)</p> <p>1. A compound represented by the formula (I) or a salt thereof: (see diagramm 1 page 393) wherein n represents an integer of 1 to 3, R represents a linear or branched alkyl group having 3 to 8 carbon atoms, a group Ra represented by the following formula: R**1 (CH₂)_k - or a group Rb represented by the following formula: (see diagramm 2 page 393) wherein k in the substituent Ra represents 0 or an integer of 1 to 3; R**1 represents a saturated cyclic alkyl group having 3 to 7 carbon atoms or a saturated condensed cyclic alkyl group having 6 to 8 carbon atoms, and the group R**1 may be substituted with a lower alkyl group having 1 to 4 carbon atoms; Q in the group Rb represents a monocyclic or bicyclic aryl group, and Q may contain 1 or 2 heteroatoms; A**1 represents a single bond or an alkylene (a) having 1 to 3 carbon atoms, and the alkylene (a) may be substituted with a lower alkyl group having 1 to 4 carbon atoms or phenyl group; A**2 represents a single bond, oxygen atom, sulfur atom, -S(O)-, -S(O)₂ -, or -N(R**4) - (wherein, when A**2 represents oxygen atom, sulfur atom, -S(O)-, -S(O)₂ -, or -N(R**4) -, A**1 represents ethylene or trimethylene); R**2 and R**3 both or each independently represent hydrogen atom, a linear or branched saturated alkyl group having 1 to 4 carbon atoms, phenyl group, fluorine atom, chlorine atom, bromine atom, trifluoromethyl group, an -OR**5 group, an -N(R**6)₂ group, an -NHCOR**7 group, or an NHSO₂ R**8 group, wherein R**4, R**6, and R**7 each independently represent hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms, and R**5 and R**8 represent a lower alkyl group having 1 to 4 carbon atoms; Z represents hydrogen atom, fluorine atom, chlorine atom, nitro group, amino group, methyl group, or an OR**9 group wherein R**9 represents hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; the substituent Ar represents a substituent selected from the group consisting of condensed bicyclic substituents of ArI, ArII, ArIII, ArIV, ArV, ArVI, ArVII, ArVIII, ArIX, ArX, ArXI, and ArXII represented by the following formulas: (see diagramm 1 page 394) (see diagramm 2 page 394) (see diagramm 3 page 394) which bind at any of the positions of a, b, c, and d on the rings, and wherein the substituent X**1 in the group ArI represents hydrogen atom, a -OR**10 group, a -N(R**11)(R**12) group, a -SO₂ R**13 group, or carboxyl group, wherein R**10 represents hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms, or a (CH₂)_i R**14 group wherein i represents an integer of 1 to 3, and R**14 represents hydroxyl group, carboxyl group, or N,N-dimethylcarbamoyl group, R**11 represents hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms, R**12 represents hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms, 2-hydroxyethyl group, a -COR**15 group, or a SO₂ R**16 group, wherein R**15 represents amino group, a lower alkyl group having 1 to 4 carbon atoms, hydroxymethyl group, aminomethyl group, dimethylaminomethyl group, phenyl group, or furyl group, and R**13 and R**16 each independently represent a lower alkyl group having 1 to 4 carbon atoms, amino group, methylamino group, or dimethylamino group; in the group ArII, W represents oxygen atom, sulfur atom, or NX**8, the substituent X**2 represents hydrogen atom, a linear or branched saturated alkyl group having 1 to 4 carbon atoms, or carboxyl group, the substituent X**3 represents hydrogen atom, a linear or branched saturated alkyl group having 1 to 4 carbon atoms, acetyl group, formyl group, carboxymethyl group, or hydroxymethyl group, the substituent X**8 represents hydrogen atom, a linear or branched saturated alkyl group having 1 to 4 carbon atoms, a saturated cyclic alkyl group having 3 to 7 carbon atoms, or a (CH₂)_j R**17 group wherein j represents an integer of 1 to 3, and R**17 represents hydroxyl group or carboxyl group; the substituent X**4 in the group ArIII represents hydrogen atom, methyl group, methoxy group, amino group, methylamino group, or dimethylamino group; in the group ArIV, X**6 represents oxygen atom, sulfur atom, or NX**9, and the substituents X**5 and X**9 both represent hydrogen atom or methyl group; the substituent X**7 in the groups ArV and ArXI represents hydrogen atom or methyl group; M in the groups ArVII and ArVIII represents sulfur atom or NX**8; the substituent X**10 in the group ArVII represents hydrogen atom, a linear or branched saturated alkyl group having 1 to 4 carbon atoms, carboxyl group, acetyl group, formyl group, or an OR**22 group (wherein, when M in the group ArVII represents sulfur atom, the substituent X**10 represents hydrogen atom or a linear or branched saturated alkyl group having 1 to 4 carbon atoms), wherein R**22 represents hydrogen atom or a lower alkyl group having 1 to 4 carbon atoms; the substituent X**11 in the groups ArVIII, ArIX, and ArX represents hydrogen atom or a linear or branched saturated alkyl group having 1 to 4 carbon atoms; and the substituent X**12 in the groups ArIX and ArX represents hydrogen atom, a linear or branched saturated alkyl group having 1 to 4 carbon atoms, or carboxyl group; and the group Y represents hydrogen atom, a lower alkyl group having 1 to 4 carbon atoms, a -(CH₂)_m N</p>

	(R**18)(R**19) group, or a -C(R**20) ₂ OC(O)A**3 R**21 group, wherein m represents an integer of 2 or 3, R**18 is the same as R**19 , or represents a saturated alkyl group binding to R**19 to form a 3- to 6-membered ring together with the nitrogen atom or forms morpholino group together with the nitrogen atom, R**19 represents methyl group, ethyl group, or propyl group, R**20 represents hydrogen atom, methyl group, ethyl group, or propyl group, R**21 represents a lower alkyl group having 1 to 4 carbon atoms, a saturated cyclic alkyl group having 3 to 6 carbon atoms, or phenyl group, and A**3 represents a single bond or oxygen atom.
UP	2004-13